1. Current literature highlights

1.1. High-affinity ligands to the α2δ subunit of voltage-gated calcium channels

Gabapentin (i) is an anticonvulsant agent used in the clinical treatment of epilepsy. Clinical studies have recently demonstrated that gabapentin is also efficacious in reducing neuropathic pain in humans and suggested that this and related gamma amino acids may represent promising new therapeutics for treatment of both neuropathic pain and anxiety. It has been postulated that the efficacy of gabapentin in reducing neuropathic pain may be a consequence of its interaction with the α2δ subunit to which it binds. Recent work has probed the α2δ binding hypothesis in order to discover a compound superior to gabapentin.¹

The approach taken involved high-throughput parallel synthesis in solution, in tandem with rapid purification techniques. This formed the basis for the synthesis of a focused library of 576 pyrrolopyridazine derivatives, of general structure (ii). The key to the synthesis was a parallel SN2Ar coupling methodology allowing rapid generation of a 1-aminopyrrolopyridazine library (transformation (iii) to (ii) in the Scheme). The library was screened in a [3H]-gabapentin binding assay against human A710 cell membranes. A number of active compounds were obtained of which one of the most potent was (iv) with an α2δ binding affinity (IC50) of 30 nM.

This work has demonstrated the use of a high-throughput parallel SN2Ar reaction, which allowed in turn rapid SAR generation around lead compounds. The library generated a series of active compounds with improved or equal potencies compared to those of the initial lead compound used in this study.

1.2. The piperazine core of tricyclic farnesyltransferase inhibitors

Farnesyltransferase (FTase) is a heterodimeric protein that transfers the isoprenoid moiety of farnesyl pyrophosphate...
(FPP) to C-terminal CAAX box sequences. CAAX prenylation is needed for activation of oncogenic Ras proteins and it is believed that Ras activity could be modulated through FTase inhibition. However, a number of studies indicate that FTase inhibitors (FTIs) can suppress the growth of transformed cells and tumours regardless of Ras activation status. Despite these apparent ambiguities, FTIs promote clinical regression of a number of solid tumour types with a modest toxicity profile when used as single agents or in combination with cytotoxic agents.

Lonafarnib (v) is an FTI currently in phase III clinical trials. Structure–activity relationships (SARs) targeting the N-1 position of the piperidine core of lonafarnib have been explored but most derivatives produce IC₅₀ values only in the micromolar range. Chemical development of tricyclic FTIs containing a piperazine core has been largely limited to substitution with either pyridine or piperidine functionalities. In order to more thoroughly understand the SAR at the piperazine core, recent work has examined the variation of 63 distinct substituents on the N-1 (R₃) position in conjunction with variation of 31 substituents at the C-2 (R₁) position.²

In this work an 11,718-member ECLiPS® (Encoded Combinatorial Library on Polymeric Support) library was synthesised in mixtures on TentaGel solid phase resin derivatised with a 4-bromomethyl-3-nitrobenzamide photolabile linker. The library was built up from coupling of a set of R₁ amines with a piperazine carboxylic acid core to deliver (vi). This was then acylated on one nitrogen (using R₃ acids), then coupled to aryl chlorides giving (vii). The library compounds were then screened in a scintillation proximity assay at a concentration of 500 nM per bead eluate. Upon screening of the library, a number of active components were discovered. Following deconvolution and re-synthesis of components within the active mixtures, one of the most potent compounds isolated was (viii) which possessed an FTase enzyme IC₅₀ of 30 nM. This work is important in that it demonstrates for the first time that substitution at R₁ is tolerated, revealing a new sub-site that can be explored through synthesis, thereby enabling new SAR to be generated.

2. A summary of the papers in this month’s issue

2.1. Solid-phase synthesis

The biomimetic formation of gramicidin S, cyclo-(d-Phe-Pro-Val-Orn-Leu)-₂, by the dimerisation and cyclisation of pentapeptide precursor without the protection of ω-amino group of the Orn residue has been examined on a solid support. The cyclisation of H-d-Phe-Pro-Val-Orn-Leu-oxime on a resin with an oxime group of 0.62 mmol/g in 1,4-dioxane directly gave gramicidin S in a 50% yield. The dimerisation-cyclisation mode on the solid support was similar to that of the biosynthesis of gramicidin S on an enzyme.³

A rapid and efficient Fmoc solid-phase synthesis of cyclic lipodepsipeptide analogue to the antibiotic fusaricidin A has been described. The synthetic approach includes resin attachment of the first amino acid via side chain, successful use of combination of four quasi-orthogonal removable protecting groups, stepwise solid-phase synthesis of linear peptide analogue, lipid tail attachment followed by depsipeptide bond formation and on-resin head-to-tail cyclisation.⁴

Phosphorodithioate-type short oligonucleotides have been efficiently synthesised using bis(2,6-dimethylphenyl) phosphorochloridate as a coupling agent on a solid support by application of the H-phosphonothioate method, where oxidation was facilitated using elemental sulphur following completion of H-phosphonothioate oligomer assembly.⁵
2.2. Solution-phase synthesis

The parallel solution-phase synthesis of two libraries of product-like compounds derived from a 1-aryltetralin privileged structure has been described.6

2.3. Scaffolds for combinatorial libraries

A new methodology for the functionalisation of scaffold molecules on solid support which does not require (partial) protection of the scaffold or a special functional group arrangement on it, has been described. Three scaffold molecules (1,3,5-tris(aminomethyl)-2,4,6-triethylbenzene, tris(2-aminoethyl)amine, and triazacyclononane) were functionalised with different groups in moderate to high yield and purity.7

Starting from the 3-aza-6,8-dioxa-bicyclo[3.2.1]octane (BTAa) scaffold, a virtual library of molecules has been generated and screened in silico against the crystal structure of the human macrophage metalloelastase (MMP-12). The molecules obtaining high scores were synthesised and the affinity for the catalytic domain of MMP-12 was experimentally proved by NMR experiments. A BTAa scaffold showed a fair inhibition potency for MMP-12 and suggests that this bicyclic scaffold may be exploited for the design of new selective matrix metalloproteinase inhibitors.8

2.4. Solid-phase supported reagents

Antimony chloride doped on hydroxyapatite (SbCl3–HAP) has been shown to be an efficient catalyst for the one-pot stereoselective synthesis of trans-pyran[3,2-c]quinolines from anilines, benzaldehydes and 3,4-dihydro-2H-pyran (DHP).9

A polynimo resin prepared by the condensation of z,z'-di-chloro-p-xylene, ethylenediamine and tris-(2-aminoethyl)amine has been successfully exploited as a quencher reagent for acids and electrophiles both in aqueous and organic solutions. This resin has applications as a solid support for peptide synthesis.10

A 5'-regioselective phosphitylation of 3',5'-OH-guanosine derivatives has been developed using a solid-supported coupling reagent with either a standard or a bulky phosphine. After oxidation into thionophosphotriester or phosphotriester by means of solid-supported oxidisers, the 5'-phosphorylated N5-i-Bu-2'-OMe guanosines were isolated in good yields (70–80%).11

Polystyrene beads bearing chiral 1,1'-bi-(2-naphthol) (BI-NOL) moieties have been readily prepared by Suzuki couplings between chiral 6-bromo-1,1'-bi-(2-naphthols) and crosslinked polystyrene beads containing phenylboronic acid residues. The new polymer-supported (PS) BINOLs were reacted with titanium tetraisopropoxide to give catalysts for the oxidation of aryl methyl thioethers using t-butyl hydroperoxide in tetrahydrofuran giving the expected sulphoxides in up to 91% ee.12

Five partly novel aryl substituted m-hydrobenzoins have been synthesised and the corresponding desymmetrised hydrobenzoin ethers evaluated as open chain chiral auxiliaries in the L-Selectride® mediated stereoselective reduction of phenylglyoxylates. Two optimised auxiliary structures were immobilised on commercially available Wang-resin and applied as a reusable solid supported chiral auxiliary in the same type of reaction.13

Two recently reported, m-hydrobenzoin derived open chain chiral auxiliaries, which were developed for application in either solution or immobilised on a solid support, have been tested in the diastereoselective addition of RZnX to phenylglyoxylates and pyruvates, resulting in diastereomeric excesses of up to >98% de.14

2.5. Novel resins, linkers and techniques

Aminomethyl-polystyrene resins have been prepared using FeCl3–nitromethane and FeCl3–benzophenone complexes as Friedel–Crafts catalysts. All the resins were highly loaded and functionalised with Rink amide linker. A comparative synthesis of the classic difficult sequence ACP (65–74) on the prepared resins by Fmoc/γ-Bu chemistry has been presented, and the target peptide of highest purity (91%) was that prepared using FeCl3–nitromethane.15

Click chemistry has been adapted for the immobilisation of various Cinchona alkaloid derivatives bearing alkyn functional groups onto azide-modified silica gel surfaces. This protocol employs very mild reaction conditions, with catalytic amounts of copper(I) iodide in acetonitrile at room temperature, ensuring complete chemical integrity of the multifunctional ligands.16

2.6. Library applications

A dynamic combinatorial library has been prepared by the metal-induced self-assembly of phenanthroline derivatives having a guest binding unit. Using ESI mass spectrometry, the binding assay identified the most effective combination of guest binding units for fullerenol binding.17

A recent paper describes the synthesis and structure-activity relationships, developed through an iterative analogue library approach, of potent and selective non-sarcosine-derived GlyT1 inhibitors.18

A series of 2-arylbenzimidazoles has been synthesised and found to bind with high affinity to the human histamine H4 receptor. Structure–activity relationships were investigated through library preparation and evaluation as well as traditional medicinal chemistry approaches, leading to the discovery of compounds with single-digit nanomolar affinity for the H4 receptor.19

Several series of low molecular weight 5-HT2A leads have been identified from an analysis of HTS data, the exploration of SAR and optimisation of one series using parallel synthesis, affording a compound with nanomolar 5-HT2A affinity.20
A library of halogenated 2-arylindolyl-3-oxocarboxamides has been prepared to develop radioligands to visualize cerebral PBR by SPECT and PET imaging. In vitro evaluation showed that most of the synthesised compounds were selective, high-affinity PBR ligands with adequate lipophilicity.11

To address the lack of specificity often observed with NADPH-dependent carbonyl reductase inhibitors, a library of bead-immobilised compounds has been screened against fluorescently labelled aldose reductase in the presence of fluorescently labelled aldehyde reductase, a non-target enzyme, to identify compounds which were aldose reductase specific. Picked beads were decoded via novel bifunctional bead mass spec-based techniques and kinetic analysis of the ten inhibitors which were identified using this protocol yielded IC50 values in the micromolar range.22

References


Further reading

Papers on combinatorial chemistry or solid-phase synthesis from other journals


Joossens, J.; Van der Veken, P.; Surpateanu, G.; Lambeir, A.-M.; El-Sayed, I.; Ali, O. M.; Augustyns, K.; Haemers, A. Diphenyl phosphate inhibitors for the urokinase-type plasminogen...


